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Resistin, Adiponectin, and Risk of Heart Failure

The Framingham Offspring Study

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Objectives We tested the association of the adipokines resistin and adiponectin with incident heart failure.

Background Abnormal concentrations of adipokines may partially explain the association between obesity and heart failure.

Methods We related circulating adipokine concentrations to the incidence of heart failure in 2,739 participants in the Framingham Offspring Study.

Results During 6 years of follow-up, 58 participants developed new-onset heart failure. In proportional hazards models (adjusting for age, sex, blood pressure, antihypertensive treatment, diabetes, smoking, total/high-density lipoprotein cholesterol ratio, prevalent coronary heart disease, valvular heart disease, left ventricular hypertrophy, and estimated glomerular filtration rate) using the lowest third of the resistin distribution as the referent, the hazard ratios for heart failure in the middle and top thirds were 2.89 (95% confidence interval [CI]: 1.05 to 7.92) and 4.01 (95% CI: 1.52 to 10.57), respectively ($p = 0.004$ for trend). Additional adjustment for body mass index, insulin resistance (measured with the homeostasis model), C-reactive protein, and B-type natriuretic peptide did not substantively weaken this association (multivariable hazard ratios [HRs]: 2.62 and 3.74, $p = 0.007$). In the maximally adjusted model, each SD increment in resistin (7.45 ng/ml) was associated with a 26% increase in heart failure risk (95% CI: 1% to 60%). Concentrations of adiponectin were not associated with heart failure (multivariable HRs: 0.87 and 0.97, $p = 0.9$).

Conclusions Increased circulating concentrations of resistin were associated with incident heart failure, even after accounting for prevalent coronary heart disease, obesity, and measures of insulin resistance and inflammation. The findings suggest a role for resistin in human disease and a novel pathway to heart failure. (J Am Coll Cardiol 2009;53:754–62) © 2009 by the American College of Cardiology Foundation

Heart failure is a common health problem that is increasing in prevalence (1). Despite improvements in treatment, heart failure remains a highly lethal disease (2). Identification of risk factors for the development of heart failure could aid development of prevention strategies. Numerous risk factors have been well established, including age, coronary heart disease (CHD), hypertension, valvular heart disease, left ventricular hypertrophy, diabetes, and obesity (3). Recent investigations have highlighted the association of overweight and lesser degrees of obesity with increased incidence of heart failure (4). Insulin resistance is likely to account for some, but not all of this association (5).

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The mechanisms by which insulin resistance and obesity promote heart failure risk remain uncertain. Proposed mechanisms include a systemic inflammatory state with increased concentrations of circulating inflammatory mediators such as C-reactive protein, plasminogen activator inhibitor-1, tumor necrosis factor-alpha, interleukin-6, angiotensinogen, vascular endothelial growth factor, and serum amyloid A3 (6). Increased circulating concentrations of

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tumor necrosis factor-α, interleukin-6, and C-reactive protein have been associated with increased incidence of heart failure (7,8).

Several novel proteins secreted by adipocytes (adipokines), including resistin and adiponectin, have pro- and anti-inflammatory properties and are correlated with concentrations of plasma cytokines (9,10). Like other inflammatory markers, greater concentrations of resistin have been associated with CHD in some (9,11–13) but not in other studies (14,15). A single, cross-sectional analysis of patients with established heart failure found that greater concentrations of resistin correlated with increased disease severity and also predicted adverse cardiac outcomes (16). However, resistin has yet to be examined as a predictor of new-onset heart failure in the community.

Concentrations of adiponectin are decreased in insulin resistance and obesity, an inverse association that suggests adiponectin may mitigate the adverse effects of circulating inflammatory mediators, as has been demonstrated in experimental models (17,18). Low concentrations of adiponectin have been associated with increased risk of CHD (19) and inconsistently related to heart failure incidence (20,21). In patients with established heart failure, low adiponectin has paradoxically been associated with decreased mortality (21,22). Thus, the role of adiponectin in the development of heart failure remains uncertain as well.

With this background in mind, we examined the association of circulating resistin and adiponectin concentrations with the development of heart failure in a community-based sample. We hypothesized that greater concentrations of resistin and lower concentrations of adiponectin would be associated with an increased risk of heart failure. Additionally, we postulated that this association would be attenuated by adjustment for associated variations in obesity, insulin resistance, and inflammation that constitute potential mediatory mechanisms.

Methods

Study participants. The Framingham Offspring Study is a community-based, prospective, observational study of cardiovascular disease and its risk factors. The study began in 1971 with the enrollment of 5,124 participants who were the children of the original Framingham Heart Study cohort and the spouses of these children. Members of the Offspring cohort are white and of mixed European ancestry (23). During the seventh examination cycle (1999 to 2001; the baseline examination for the present study), 3,539 participants underwent standardized medical history, physical examination, 12-lead electrocardiogram, and analysis of fasting blood samples. We excluded 32 participants with prevalent heart failure at baseline. Because we began measuring adipokine concentrations part way through the seventh examination cycle, an additional 768 participants with missing adipokine concentrations were excluded, leaving 2,739 individuals for analysis. Participants not included in the analysis were older with slightly greater levels of CHD risk factors than those included. The study protocol was approved by the Institutional Review Board of the Boston University School of Medicine, and all participants provided written informed consent.

Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
HDL = high-density lipoprotein
HOMA-IR = insulin resistance measured with the homeostasis model
HR = hazard ratio
UACR = urine albumin/creatinine ratio

Covariate definitions and laboratory methods. We measured height, weight, and waist circumference by using a standardized protocol. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). The examination blood pressure was taken as the mean of 2 physician-obtained measurements after the participant had been seated for at least 5 min. We defined diabetes as a fasting plasma glucose >125 mg/dl or treatment with blood glucose-lowering medications. Coronary heart disease was defined by standard Framingham Heart Study criteria as any of new-onset angina, coronary insufficiency, or fatal or nonfatal myocardial infarction. We defined valvular heart disease by the presence of a systolic murmur of grade 3/6 or greater or any diastolic murmur (24). We used a continuously distributed electrocardiographic metric of left ventricular hypertrophy by summing the voltages of the R-wave in lead aVL and the S-wave in lead V_3 (25). Those who reported smoking cigarettes regularly during the year before the examination were considered current smokers.

Participants fasted overnight to provide blood specimens. Samples were frozen at −80°C until assay. Laboratory methods for creatinine, glucose, insulin, and lipid assays have been published previously (26,27). Assay coefficients of variation were <3% for glucose and <10% for insulin. We calculated insulin resistance with the homeostasis model using the following validated formula: HOMA-IR = (fasting glucose [mmol/l] × fasting insulin [μU/ml])/22.5 (28,29). C-reactive protein was measured with an immunoprecipitation assay (IncStar, Stillwater, Minnesota). We estimated the glomerular filtration rate as follows: (186 × [serum creatinine] − 1.154) × ([age] − 0.203) × (0.742 if female) (30). The urine albumin/creatinine ratio (UACR) was assessed at exam 6 from a single void urine sample. The urine albumin concentration was measured by immunoturbimetry (Tina-quant Albumin assay, Roche Diagnostics, Indianapolis, Indiana) and the urine creatinine concentration by the use of a modified Jaffe method. Plasma interleukin-6, tumor necrosis factor-alpha, resistin, and total adiponectin were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota) (7). Intra-assay coefficients of variation were 3.1% for interleukin-6, 6.6% for tumor necrosis factor-α, 5.8% for

adiponectin, and 9.0% for resistin. Plasma B-type natriuretic peptide was not measured at examination cycle 7, so we used measurements from examination cycle 6 using a high-sensitivity, noncompetitive immunoradiometric assay (Shionogi, Osaka, Japan) (8).

Definition of heart failure. All new heart failure events occurring from baseline through end of follow-up in December 2005 were adjudicated by a panel of 3 physicians, according to previously published Framingham criteria (31). Specifically, the simultaneous presence of either 2 major or 1 major plus 2 minor criteria, in the absence of an alternative explanation for the symptoms and signs, was required to make the diagnosis of heart failure. Major criteria included paroxysmal nocturnal dyspnea, orthopnea, jugular venous distension, hepatojugular reflux, pulmonary rales, radiographic evidence of cardiomegaly, acute pulmonary edema, third heart sound, central venous pressure >16 cm of water, and weight loss >4.5 kg during the first 5 days of treatment for suspected heart failure. Minor criteria included bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, and heart rate >120 beats/min. Of 58 participants with new heart failure events, 54 were hospitalized with heart failure and 4 were not hospitalized but were diagnosed with heart failure based on physician office visits.

Statistical analysis. We classified participants into thirds of the distribution of resistin and adiponectin. The primary analyses were conducted for pooled sexes because of low statistical power for sex-specific analyses given the modest number of heart failure events on follow-up. We used analysis of variance or Mantel-Haenszel tests of trend to assess differences in mean risk factor levels or proportions across adipokine strata, and Spearman correlation coefficients to assess correlations among risk factors. For analysis of variance tests, levels of HOMA-IR, C-reactive protein, B-type natriuretic peptide, and UACR were log-transformed to reduce skewness; we present the results by taking the anti-logarithm for ease of interpretation. We constructed Kaplan-Meier curves to illustrate survival free of heart failure for each adipokine stratum and tested differences in survival across strata with the log-rank test. We used a nested series of Cox proportional hazards regression models (after confirming the assumption of proportionality of hazards) to test the hypothesis that greater concentrations of resistin and lower concentrations of adiponectin were associated with an increased risk of heart failure after adjustment for potentially confounding heart failure risk factors. Cox models provided hazard ratios (HRs) and 95% confidence intervals (CIs) for incident heart failure conditioned on baseline exposures. Models testing incidence of heart failure across increasing thirds of adipokines were adjusted hierarchically for: 1) age and sex; 2) age, sex, systolic blood pressure, antihypertensive treatment, diabetes, smoking, total/high-density lipoprotein (HDL) cholesterol ratio, prevalent coronary heart disease, valvular heart disease, left ventricular hypertrophy, and estimated glomerular filtration rate; and 3) the variables in model 2 and BMI, HOMA-IR, C-reactive protein, and B-type natriuretic peptide, individually and together in a maximally adjusted model. Tests of trend across HRs were assessed in models with the use of ordinal increments to represent adipokine strata. We further examined dose-response relations of adipokines and heart failure in the maximally adjusted model using penalized splines (32), and in multivariable adjusted analyses, we tested the association of heart failure with adipokines as continuously distributed, using per SD increase (7.45 ng/ml for resistin and 6.32 μg/ml for adiponectin) as the unit of exposure.

Subsidiary analyses. Because CHD at baseline or a new CHD event over follow-up would be expected to be a potent risk factor for new-onset heart failure, in additional subsidiary analyses we excluded all baseline and new cases of CHD (92 cases) occurring during the course of follow-up. Given 58 heart failure events, the full model with 15 predictor variables may have been overparameterized. To address this concern, we repeated the analyses in models that substituted the Framingham coronary heart disease risk score for its individual components (age, systolic blood pressure, antihypertensive treatment, diabetes, current cigarette smoking, and total and HDL cholesterol) (33). Because interleukin-6 and tumor necrosis factor-alpha are inflammatory markers that have been associated with heart failure, we substituted each one for C-reactive protein (7).

In addition to accounting for renal function using estimated glomerular filtration rate, we also adjusted models for UACR. However, UACR was measured 4 years before the other baseline measures in this study, and data were not complete (2,241 had UACR levels), so results should be interpreted with caution. We also repeated the analyses using waist circumference instead of BMI, because a larger waist circumference may be more reflective of abnormal adipocyte function and has been shown to predict cardiovascular events in normal-weight, overweight, and mildly obese subjects (34). Although sex differences were not a hypothesis of the present investigation, we repeated our analyses using sex-specific thirds of the adipokine distributions; results were identical to those of the pooled-sex analyses, so we present only the latter. Finally, we assessed the association of adipokine levels with incident CHD, adjusted as in Model 2, with prevalent cases of CHD removed from the analysis. Analyses were performed using SAS software (version 8.1, SAS Institute, Cary, North Carolina). We considered p values <0.05 to indicate statistical significance.

Results

Baseline characteristics. Characteristics of the study participants across strata of resistin and adiponectin are displayed in Table 1, and the frequency distribution of participants by concentrations of resistin and adiponectin are displayed in Figures 1E and 1F. The prevalence of common

Table 1 Baseline Characteristics of Study Participants by Thirds of the Adipokine Distributions*

	Resistin				Adiponectin			
	Third 1, Range 1.2–10.9 (ng/ml)	Third 2, Range 11.0–14.9 (ng/ml)	Third 3, Range 15.0–110.0 (ng/ml)	p Value	Third 1, Range 0.7–6.4 (μg/ml)	Third 2, Range 6.5–11.0 (μg/ml)	Third 3, Range 11.1–59.9 (μg/ml)	p Value
n	904	923	912		920	900	919	
Female (%)	54	53	53	0.9	29	52	79	<0.0001
Age (yrs)	60 (9)	61 (9)	63 (10)	<0.0001	60 (10)	61 (9)	62 (9)	<0.0001
Systolic blood pressure (mm Hg)	126 (19)	126 (19)	130 (19)	<0.0001	128 (17)	127 (19)	126 (20)	0.09
Treatment with antihypertensive medications (%)	26	32	42	<0.0001	38	34	28	<0.0001
Type 2 diabetes (%)	8.1	10.0	15.0	<0.0001	17.7	11.8	3.6	<0.0001
Current cigarette smoking (%)	13	12	15	0.3	15	13	12	0.4
Serum total/high-density lipoprotein cholesterol ratio	3.8 (1.2)	4.1 (1.4)	4.2 (1.3)	<0.0001	4.7 (1.4)	4.1 (1.1)	3.3 (1.0)	<0.0001
Baseline prevalent coronary heart disease (%)	8.3	6.9	10.1	0.05	12.1	8.2	5.0	<0.0001
Valvular heart disease (%)	1.8	2.3	3.6	0.05	2.1	2.5	3.1	0.4
Electrocardiographic left ventricular hypertrophy (mm)	12.2 (5.1)	12.5 (5.3)	12.9 (5.0)	0.04	13.7 (5.1)	12.5 (5.0)	11.4 (5.2)	<0.0001
Body mass index (kg/m^2)	27 (5)	28 (5)	29 (6)	<0.0001	30 (5)	29 (5)	26 (5)	<0.0001
Waist circumference (cm)	97 (13)	100 (14)	103 (14)	<0.0001	105 (13)	101 (13)	94 (14)	<0.0001
Insulin resistance with the homeostasis model†	3.2 (1.9)	3.6 (2.0)	4.0 (1.9)	<0.0001	5.0 (1.9)	3.6 (1.8)	2.6 (1.7)	<0.0001
C-reactive protein (mg/ml)†	2.8 (3.2)	4.0 (5.2)	6.1 (12.1)	<0.0001	4.5 (6.3)	4.9 (10.9)	3.6 (5.8)	0.004
Plasma B-type natriuretic peptide (pg/ml)†	13 (17)	15 (18)	17 (23)	0.0004	13 (19)	15 (21)	18 (19)	<0.0001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	89 (18)	85 (18)	80 (21)	<0.0001	85 (18)	85 (20)	84 (20)	0.2
Urine albumin/creatinine ratio (mg/g)†	5.0 (5.1)	5.6 (4.9)	6.8 (5.5)	0.002	4.6 (5.4)	5.7 (5.4)	7.3 (4.5)	<0.0001
Adiponectin (μg/ml)†	8.9 (1.9)	8.4 (1.9)	8.0 (1.3)	0.0008	—	—	—	—
Resistin (ng/ml)†	—	—	—	—	13.6 (1.5)	13.1 (1.5)	12.4 (1.5)	<0.0001

*p values indicate significance for trend across strata of resistin. †Antilogarithm. Standard deviations are in parenthesis.

heart failure risk factors increased with increasing concentrations of resistin and decreased with increasing concentrations of adiponectin. Levels of BMI, waist circumference, HOMA-IR, and C-reactive protein were positively correlated with concentrations of resistin and inversely correlated with concentrations of adiponectin (Table 2). Concentrations of resistin and adiponectin were inversely correlated with each other.

Adipokines and heart failure risk. Fifty-eight participants (25 women; 19 with CHD at baseline) developed new-onset heart failure over a mean follow-up of 6 years (cumulative incidence, 2.12%). Survival free of heart failure decreased in greater strata compared with lower strata of resistin ($p < 0.0001$) (Fig. 1A). The HR for heart failure increased across strata of resistin, adjusted for age and sex (Table 3). Increased risk associated with greater resistin concentrations persisted after further adjustment for systolic blood pressure, antihypertensive treatment, diabetes, smoking, total/HDL cholesterol ratio, prevalent CHD, valvular heart disease, left ventricular hypertrophy, and estimated glomerular filtration rate. The resistin-heart failure association was maintained after further adjustment for BMI, HOMA-IR, C-reactive protein, and B-type natriuretic peptide (Table 3). Analyses of splines modeling resistin as a continuous variable and using the maximally adjusted model suggested a linear dose response relationship over the lower end of the resistin distribution where the majority of participants contributed data, arguing against outlying values driving the association (Fig. 1C). Modeled as a continuous covariate, the HRs per SD increment in resistin were 1.45 (95% CI: 1.16 to 1.82), 1.36 (95% CI: 1.09 to 1.69), and 1.26 (95% CI: 0.99 to 1.60) after adjustment as in models 1, 2, and 3E, respectively.

Adiponectin was not associated with incident heart failure in any of the models examined (Figs. 1B and 1D, Table 3). With 58 heart failure events, our investigation had 80% power at an alpha of 0.05 to detect an HR for heart failure as small as 0.39 for the greatest adiponectin third compared with the lowest. Continuously distributed concentrations of adiponectin were not associated with risk of heart failure either; in the maximally adjusted model, the HR per SD increase was 0.96 (95% CI: 0.67 to 1.36).

Subsidiary analyses. After exclusion of 231 baseline and 92 new cases of CHD occurring during the course of follow-up, there remained 26 new cases of heart failure for analysis. Exclusion of all CHD from the maximally adjusted model

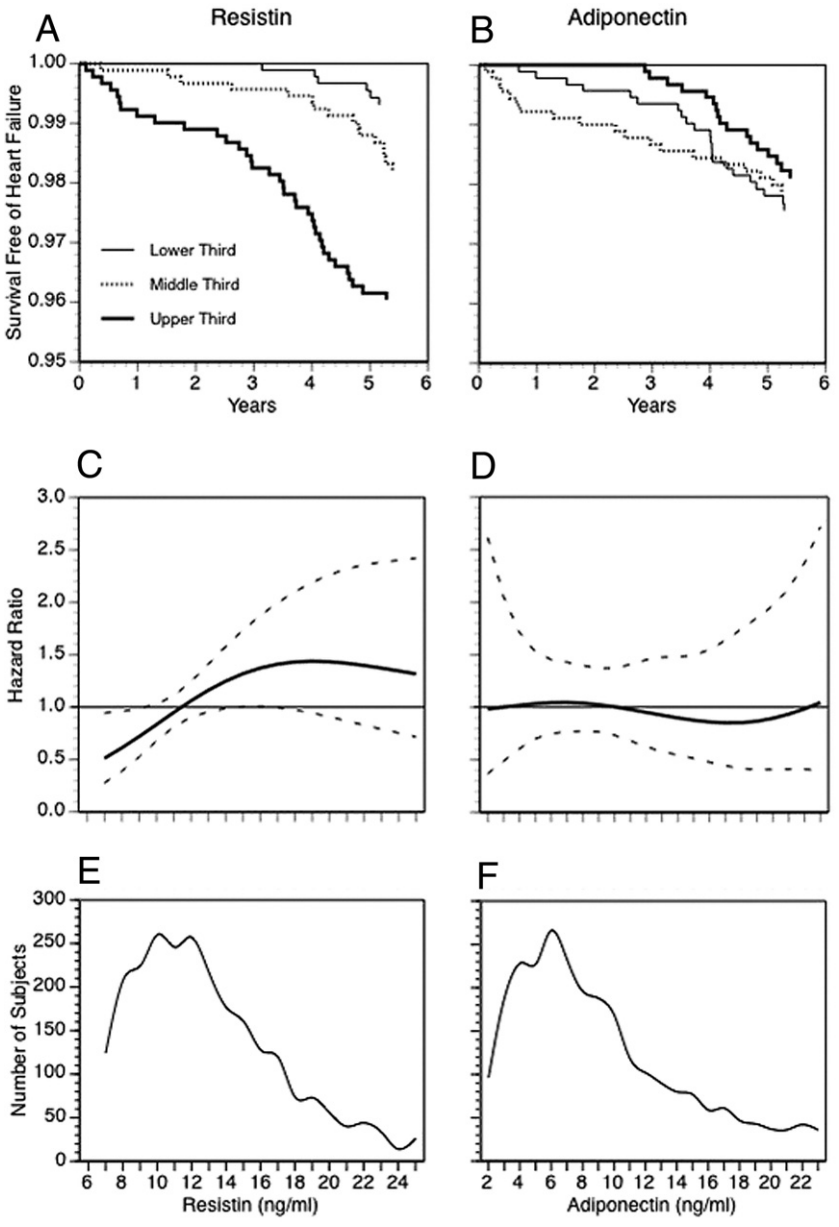

Figure 1 **Heart Failure Free Survival by Adipokine Concentration**

(A and B) Kaplan-Meier curves are shown for survival free of heart failure according to baseline thirds of resistin and adiponectin (log-rank $p < 0.0001$ for resistin, $p = 0.7$ for adiponectin). **(C and D)** Dose-response relationships between resistin and adiponectin and heart failure are illustrated with generalized additive Cox models (maximally adjusted as in Model 3E) (Table 3) using penalized splines. **Dashed lines** represent 95% confidence limits of the resulting hazard ratios. **(E and F)** Histograms illustrate the frequency distribution of study subjects across concentrations of resistin and adiponectin. There is a linear dose-response relationship of resistin with risk of heart failure across the range where the greatest number of subjects contribute information on resistin concentration.

did not substantively alter the results (Table 3). Similarly, substituting the Framingham coronary heart disease risk score for its individual components did not alter our results; for resistin, HR: 2.81 (95% CI: 1.02 to 7.75) and 4.20 (95% CI: 1.62 to 10.94) in the second and third strata of model 3E, respectively ($p = 0.002$ for trend). Adjustment for interleukin-6 or tumor necrosis factor-alpha instead of C-reactive protein did not significantly change results either. For instance, substituting interleukin-6 for C-reactive protein in model 3E yielded an HR for resistin in the top versus bottom third of 3.82 (95% CI: 1.46 to 10.03; $p = 0.005$), and substituting tumor necrosis factor-alpha for C-reactive protein yielded an HR of 4.11 (95% CI: 1.56 to 10.08; $p = 0.002$). Further adjustment of model 3E for UACR did not alter the results; the HR for resistin in the middle third was 4.31 (95% CI: 1.23 to 15.13) and in the

Table 2 Relation of Age- and Sex-Adjusted Levels of Resistin and Adiponectin to Each Other and to HOMA-IR, CRP, and BNP

	Resistin (ng/ml)		Adiponectin (μg/ml)	
	Spearman Rank Correlation Coefficient	p Value	Spearman Rank Correlation Coefficient	p Value
Body mass index (kg/m^2)	0.16	<0.0001	−0.33	<0.0001
Waist circumference (cm)	0.17	<0.0001	−0.35	<0.0001
Insulin resistance measured with the homeostasis model	0.15	<0.0001	−0.43	<0.0001
CRP (mg/ml)	0.22	<0.0001	−0.12	<0.0001
Plasma BNP (pg/ml)	0.07	0.0002	0.24	<0.0001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	−0.22	<0.0001	−0.04	0.03
Urine albumin/creatinine ratio (mg/g)	0.06	0.003	0.16	<0.0001
Adiponectin (μg/ml)	−0.09	<0.0001	—	—
Resistin (ng/ml)	—	—	−0.09	<0.0001

Spearman rank correlation coefficients are provided for the correlation between adipokine levels and antilogarithm of variables. p values were calculated with the use of analysis of variance.
BNP = B-type natriuretic peptide; CRP = C-reactive protein; HOMA-IR = insulin resistance measured with the homeostasis model.

top third 5.29 (95% CI: 1.53 to 18.23; p = 0.008). Substituting waist circumference for BMI also yielded similar results. Using waist circumference in model 3A, we found that the HR for resistin in the top versus bottom third was 4.02 (95% CI: 1.55 to 10.42; p = 0.003) and in model 3E was 3.80 (95% CI: 1.45 to 9.98; p = 0.005). Adiponectin remained unassociated with heart failure after excluding CHD, substituting the Framingham coronary heart disease risk score for its individual components, substituting interleukin-6 for C-reactive protein, substituting tumor necrosis factor-alpha for C-reactive protein, adding UACR, substituting waist circumference for BMI, and using sex-specific thirds (p = 0.6, 0.4, 0.8, 0.8, 0.9, 0.9, and 0.2 for trends across HR, respectively).

Neither resistin nor adiponectin were associated with incident CHD. For example, when adjusted as in model 2, the HR for CHD in the middle third of the resistin distribution was 0.76 (95% CI: 0.44 to 1.30) and in the top third 0.82 (95% CI: 0.49 to 1.38) (p = 0.5 for trend). For adiponectin, the HR for CHD in the middle third of the distribution was 0.73 (95% CI: 0.43 to 1.22) and in the top third was 0.70 (95% CI: 0.37 to 1.32) (p = 0.2 for trend).

Discussion

Principal findings. We observed that greater circulating resistin was strongly associated with increased risk of new-onset heart failure during 6 years of follow-up of a community-based sample. The association of resistin with

Table 3 Nested Cox Proportional Hazard Models Testing the Incidence of Heart Failure Across Adipokine Strata

	Resistin (Third)				Adiponectin (Third)			
	1	2	3	p Value	1	2	3	p Value
Number of heart failure events	6	16	36		22	19	17	
Model 1*	1.00	2.22 (0.87–5.69)	3.91 (1.63–9.35)	0.0008	1.00	0.84 (0.45–1.57)	0.64 (0.32–1.27)	0.2
Model 2†	1.00	2.89 (1.05–7.92)	4.01 (1.52–10.57)	0.004	1.00	0.90 (0.47–1.70)	0.79 (0.36–1.76)	0.6
Model 3A: Model 2 + BMI	1.00	2.77 (1.01–7.63)	3.73 (1.41–9.87)	0.007	1.00	0.93 (0.49–1.76)	0.89 (0.40–1.97)	0.8
Model 3B: Model 2 + HOMA-IR	1.00	2.56 (0.92–7.09)	3.81 (1.44–10.09)	0.005	1.00	1.03 (0.53–1.99)	1.04 (0.45–2.39)	0.9
Model 3C: Model 2 + CRP	1.00	2.86 (1.04–7.86)	3.91 (1.47–10.36)	0.005	1.00	0.88 (0.47–1.67)	0.79 (0.36–1.75)	0.6
Model 3D: Model 2 + BNP	1.00	2.93 (1.07–8.05)	4.06 (1.54–10.73)	0.004	1.00	0.80 (0.41–1.53)	0.72 (0.32–1.60)	0.4
Model 3E: Model 2 + BMI + HOMA-IR + CRP + BNP	1.00	2.62 (0.95–7.27)	3.74 (1.40–9.99)	0.007	1.00	0.87 (0.44–1.73)	0.97 (0.42–2.22)	0.9
Model 3F: Model 3E excluding participants with CHD at baseline or during follow-up	1.00	2.87 (0.57–14.52)	5.20 (1.08–25.13)	0.03	1.00	1.39 (0.46–4.26)	1.38 (0.39–4.90)	0.6

Hazard ratios for incident heart failure are provided with confidence intervals in parentheses. p values indicate significance for trend across strata of adipokine. *Adjusted for age and sex. †Adjusted for age, sex, systolic blood pressure, antihypertensive treatment, diabetes, smoking, total/high-density lipoprotein cholesterol ratio, prevalent CHD, valvular heart disease, left ventricular hypertrophy, and estimated glomerular filtration rate.
BMI = body mass index; CHD = coronary heart disease; other abbreviations as in Table 2.

heart failure persisted after adjustment for established heart failure risk factors, obesity, markers of insulin resistance and inflammation, and concentrations of B-type natriuretic peptide and after exclusion of prevalent and incident CHD. We did not find that either lower or higher concentrations of adiponectin were associated with new-onset heart failure.

Possible mechanisms. Little is currently understood about the role of resistin in the pathophysiology of cardiovascular diseases. In cross-sectional analysis, resistin has been shown to be associated with the degree of atherosclerosis in humans, as measured by coronary artery calcification (9). In a case-control study of 185 women with angiographically confirmed CHD and 227 population-based controls, the multivariable risk factor-adjusted odds ratio for CHD for women in the greatest compared with lowest quintile of plasma resistin concentrations was 3.19 (95% CI: 1.44 to 7.10, $p = 0.001$) but, after adjustment for plasma C-reactive protein concentrations, the association was no longer significant (odds ratio: 1.80; 95% CI: 0.69 to 4.69; $p = 0.23$) (11). These findings suggest the hypothesis that increased resistin could lead to heart failure by promoting CHD with subsequent ischemic left ventricular dysfunction, perhaps mediated by vascular inflammatory processes. However, in our analysis, adjustment for baseline CHD or exclusion of baseline and incident CHD events did not weaken the association between resistin and heart failure, suggesting that resistin-associated CHD is not the principal mechanism mediating the association with risk of heart failure.

Resistin is expressed by adipocytes in mice, where it has been shown to increase resistance to insulin (hence its name) (35,36). In humans, resistin is expressed in adipocytes, and to an even greater extent in macrophages (37). Resistin has been associated with markers of inflammation, including C-reactive protein, tumor necrosis factor-alpha, and interleukin-6, which have in turn been shown to predict heart failure incidence (7,9). This suggests that resistin may lead to heart failure by promoting insulin resistance and inflammation. In our analysis, greater concentrations of resistin were associated with greater degrees of insulin resistance and greater concentrations of C-reactive protein at baseline. However, adjustment for insulin resistance and inflammatory markers did not attenuate the association of resistin with heart failure, and resistin appeared to add to the risk of heart failure associated with obesity, insulin resistance, and inflammation. The data suggest that resistin may promote heart failure via mechanisms independent of insulin resistance and inflammation.

Neither high nor low concentrations of adiponectin were associated with new-onset heart failure in our study. The role of adiponectin in the pathophysiology of cardiovascular diseases is likely complex. Whereas low concentrations of adiponectin have been associated with increased risk of incident CHD in healthy participants (19), high concentrations of adiponectin have been associated with increased severity of disease and adverse outcomes in patients with established heart failure, presumably serving as a marker of cachexia observed in advanced disease (21,22,38). Although 1 cross-sectional study showed adiponectin concentrations to be greater in patients with heart failure compared with control patients (21), a prospective cohort study of elderly, Swedish men failed to detect an association between adiponectin concentrations and heart failure incidence (20).

Obesity may contribute to heart failure by additional mechanisms independent of adipokine signaling, including neurohormonal activation and increased oxidative stress (39,40), infiltration of myocytes with free fatty acids (41), and B-type natriuretic peptide depletion (42). Obesity is also associated with CHD morbidity and mortality (43), but we accounted for this possibility by removing prevalent and incident cases of CHD in subsidiary analyses.

Strengths and limitations. The strengths of our study include a large, community-based sample assessed in which we used standardized clinical measures and biomarker assays with good precision. Further, we used standardized methods for ascertainment of heart failure cases; 93% were events that led to hospitalization. The adiponectin assay used in the current investigation measured total adiponectin. It has been suggested that high-molecular weight adiponectin may be the more biologically active form. For example, when compared with total adiponectin, high-molecular weight has been more strongly associated with insulin resistance (44), metabolic syndrome (45), and the presence of coronary artery disease in diabetic patients (46). However, other evidence suggests that total adiponectin may be more strongly associated with insulin sensitivity and lipid profile, both at baseline and in response to physical training (47). It is thus unclear whether high-molecular weight adiponectin is more biologically relevant than total adiponectin. It is also possible that a small association between adiponectin and heart failure was not detected secondary to power limitations, especially in the subsidiary analysis excluding participants with baseline or incident CHD, where the number of end points was particularly limited. Additionally, our study demonstrated an association between resistin and heart failure but does not establish causality. The ability to speculate and gain insight into the potential mechanisms linking resistin and heart failure is limited by the small number of end points, particularly when participants with prevalent CHD were excluded. Finally, our study sample was almost exclusively white and middle-aged to elderly, limiting generalizability of these findings to other ethnic and age groups.

Conclusions

In our community-based sample, we found that increased plasma concentrations of resistin were associated with subsequent development of heart failure even after accounting for obesity, insulin resistance, inflammation, and concurrent and incident CHD. Levels of adiponectin were not associated with incident heart failure. The specific mechanism

whereby resistin promotes heart failure remains to be elucidated, but our findings suggest that novel mechanisms promoting heart failure remain yet to be discovered.

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